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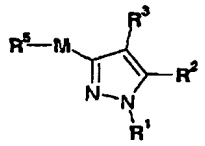
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(54) Title: DERIVATIVES OF 3-HYDROXY-4-(CYCLYL-ALKYLAMINOALKYL)-5-PHENYL-1H-PYRAZOLE AS ANTAGONISTS OF THE GONADOTROPIN RELEASING HORMONE (GNRH) FOR USE IN THE TREATMENT OF SEX HORMONE RELATED CONDITIONS, SUCH AS PROSTATIC OF UTERINE CANCER



(I)

(57) Abstract: The invention relates to a group of novel pyrazole compounds of Formula (I): wherein: R^1, R^2, R^3, M and R^5 are as defined in the specification, which are useful as gonadotrophin releasing hormone antagonists. The invention also relates to pharmaceutical formulations of said compounds, methods of treatment using said compounds and to processes for the preparation of said compounds.

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INTERNATIONAL SEARCH REPORT

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PCT/GB 03/03633

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4155 A61K31/4439 A61K31/4196 A61K31/496 A61K31/5377
A61K31/541 A61K31/506 A61K31/497 A61K31/4725 C07D401/12
C07D231/20 C07D403/12 C07D413/12 C07D417/12 C07D409/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, EPO-Internal, CHEM ABS Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 31072 A (SEARLE & CO (US)) 2 June 2000 (2000-06-02) examples 32-38,40,86 formulae IIa, IIb page 1, line 9	1-10,12, 13,16
X	WO 00 31063 A (SEARLE & CO (US)) 2 June 2000 (2000-06-02) formula 109, page 206 examples A-440-446,A-448	1-10,12, 13,16

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Date of the actual completion of the international search	Date of mailing of the international search report
21 November 2003	03/02/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Cortés, J

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INTERNATIONAL SEARCH REPORT

Internatio lication No
PCT/GB 03/03633

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D491/04 C07D405/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 10 287655 A (KAKEN PHARMA CO LTD (JP)) 27 October 1998 (1998-10-27) 5th to 8th compound in 1st row of table on page 5 17th to 19th compound in 2nd row of table on page 6 all compounds in 1st row of table o page 7 1st to 9th and 20th to 24th compound in 2nd row of page 7 compounds 54 and 56, page 16 formula I & PAJ abstract — -/—	1-8,10, 12,13,16

[X] Further documents are listed in the continuation of box C.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 November 2003	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cortés, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB 03/03633

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; O'CALLAGHAN, C. N.: "Synthesis of ethyl 3-oxo-4-pyrazolidinecarboxylates" retrieved from STN Database accession no. 77:61875 XP002261638 abstract & JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1: ORGANIC AND BIO-ORGANIC CHEMISTRY (1972-1999) (1972), (11), 1416-19 ,	1-10,12, 13,16
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MOHAREB, RAFAT M. ET AL: "The reaction of 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo'b! thiophene with diethyl malonate: synthesis of coumarin, pyridine, and thiazole derivatives" retrieved from STN Database accession no. 135:92599 XP002261639 abstract & HETEROATOM CHEMISTRY (2001), 12(3), 168-175 ,	1-10,12, 13,16
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INTERNATIONAL SEARCH REPORT

Internation cation No
PCT/GB 03/03633

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MUSTAFA, AHMED ET AL: "Reactions of substituted coumarins, furocoumarins, and khellinonestyryl derivatives with hydrazine and phenylhydrazine" retrieved from STN Database accession no. 65:20701 XP002261641 abstract & JUSTUS LIEBIGS ANNALEN DER CHEMIE (1966), 692, 166-73 ,	1-10,12, 13,16
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INTERNATIONAL SEARCH REPORT

Interr application No.
PCT/GB 03/03633

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-16 (partly)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-16 (partly)

The claimed compounds are widely known pharmaceutically active compounds.

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).

For these reasons, a meaningful search over the whole breadth of the claims is impossible.

Consequently, the search has been restricted to a generic group defined by the structural features of the examples, i.e. to compounds wherein:

R2 is optionally substituted phenyl,
M is -(CH2)0-2-O- and
A is one of the options (i) to (iv) in claim 1

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

information on patent family members

Intern dication No
PCT/GB 03/03633

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